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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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Helen C. Lockhart, Ph.D.
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
11/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. No claims have been amended, canceled, or added.

2. Claims 42-53, 59-69, 71-73, and 75-80 are under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on October 14, 2008 was filed after the mailing date of the first action on the merits on February 4, 2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Rejections Maintained

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 42-53, 59-69, 71-73, and 75-80 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

Applicant's response filed August 4, 2008 has been carefully considered but they are deemed not to be persuasive. The response states that in response to the prior

office action Applicant presented some evidence of the state of the art at the time the application was filed and also provided a discussion of how such art related to the data that was provided in the specification. Applicant asserts that in view of what was known in the art at the time of the invention and the data and teachings provided in the specification, one of ordinary skill in the art would have had a reasonable expectation that CpG oligonucleotides were useful for treating cancer (see response page 7).

In response to this argument, as set forth in the previous office action, the specification discloses the immunostimulatory activity of oligonucleotides containing an unmethylated CpG dinucleotide. However, such disclosure does not enable a skilled artisan to treat cancer comprising administering oligonucleotides containing an unmethylated CpG dinucleotide. The state of the art is such that there is a high degree of unpredictability in the treatment of cancers comprising administering oligonucleotides containing an unmethylated CpG dinucleotide. The claims are drawn to a method of treatment of cancer comprising a huge genus of oligonucleotides containing an unmethylated CpG dinucleotide. In view of the unpredictability in the art, with regard to the treatment of cancers, one of ordinary skill in art would require an undue experimentation to practice the claimed method with all the oligonucleotides encompassed within the claims. Further, the claims require administering an effective amount of the oligonucleotides ranging from 8 to 100 nucleotides. Thus, the process of achieving a desirable effective amount for administration in vivo for each and every one of the oligonucleotides encompassed within the huge genus of oligonucleotides encompassed by the claims is a very lengthy and complicated process; because, the

prior art recognizes that unlike the situation in vitro, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist in vitro. Therefore, prediction of drug effects in cancer patients based solely on in vitro data is not reliable and further evaluation in animal tumor systems is essential." Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In deciding In re Fisher, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005 (CA FC 1997).

Supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. MPEP 2164.05(a) states that if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the

application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Hence, as stated in the previous office actions, the studies published well after the filing date of the instant application clearly recognize the obstacles in treating cancers comprising oligonucleotides containing an unmethylated CpG dinucleotide and address the unpredictability.

Applicant has directed arguments separately to references post-filing and at the time of filing of the instant application. In direct response to the state of the art at the time the application was filed, applicant states "at the time the patent application was filed it was known in the art that induction of interferon-g, IL-12, IL-6, and NK cell activation was useful in the treatment of cancer (see response page 7). None of these references discuss administration of CpG oligonucleotides or any form of nucleotide for the treatment of cancer. Specifically, Trinchieri, et al. administer cancer cells, Brunda, et al. administer IL-12, US Pat 4,883,662 administers a Parvovirus, and Hayashi, et al. administers BCG-CWS. Each of these cancer therapies involve different components of the immune system and different mechanisms of inducing an immune response.

The description and the data found in the specification is not sufficient, because the specification does not teach those skilled in the art how to make and use the full scope of the claimed invention, which is the treatment of cancer comprising administering CpG immunostimulatory oligonucleotides comprising 8 to 100 nucleotides in length, without undue experimentation. The examples in the specification show that

unmethylated CpG are effective at stimulating B-cell proliferation, cytokine secretion for example; however, based on the undue experimentation necessary in understanding the treatment of cancer comprising CpG molecules as taught by the prior art, the amount of additional experimentation is deemed to be undue. In order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonucleotides would not work for treating any cancer.

With regard to CpG in the treatment of cancers, Weiner (Leukocyte Biology, 68(4):455-463, 2000) indicates that there is therapeutic potential in cancer treatment for CpG as an immune adjuvant (Table 1) and that there are a number of scenarios where CpG could be used as a component of cancer immunotherapy, each of these areas is under intensive investigation (p. 458, col. 1). Studies in a tumor model (38C13 murine lymphoma) indicate that CpG was just as effective as CFA at inducing an antigen-specific antibody response (p. 458, col. 2). Weiner teaches that "[P]reliminary studies suggest CpG ODN can be effective in a variety of scenarios when used alone or in combination with other agents. Despite this promise we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG ODN. All CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Most importantly, we have not yet explored their clinical effects. Further work with CpG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (p. 461, col. 1) Krieg

et al (Nature, 374:546-549, 1995) teaches that CpG has NK-stimulating properties and suggest that it can be used in immunotherapy of tumors, yet Krieg et al also indicates that many or even most types of tumors are relatively resistant to NK- mediated lysis (p. 117, col. 2). Ballas et al (The Journal of Immunology, 167:4878- 4886, 2001) teaches that the selection of optimal CpG ODN for cancer immunotherapy depends upon a careful analysis of the cellular specificities of various CpG motifs and an understanding of the cellular mechanisms responsible for the antitumor activity in a particular tumor (abstract). Ballas et al teaches that a single CpG ODN cannot be used to treat all cancers and tumors. Although several CpG ODN were active as sole immunotherapeutic agents in two tumor models, different motifs were optimal in each model. CpG ODN 1585 was optimal against B16 melanoma and its effects were dependent on NK cells. CpG ODN 1826 was optimal in a lymphoma model and its effects appeared to require NK (early) and T cells (late). These results illustrate that the potent distinct CpG motifs can be custom-tailored for each desired immune effect (p. 4878, col. 2; see also p. 4885, col. 1). Agrawal et al (TRENDS in Molecular Medicine, 2002, 8/3:114-120) also teaches that different effects are observed with different CpG ODNs.

The description and the data found in the specification is not sufficient, because the specification does not teach those skilled in the art how to make and use the full scope of the claimed invention, which is the treatment of cancer comprising administering CpG immunostimulatory oligonucleotides comprising 8 to 100 nucleotides in length, without undue experimentation. The examples in the specification show that

unmethylated CpG are effective at stimulating B-cell proliferation, cytokine secretion for example; however, based on the undue experimentation necessary in understanding the treatment of cancer comprising CpG molecules as taught by the prior art, the amount of additional experimentation is deemed to be undue. In order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonulceotides would not work for treating any cancer.

Thus, in conclusion, the applicant is reminded that the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide; the breadth of the claims as mentioned above; the limited number of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed vaccine composition is undue.

The references clearly point towards the undue experimentation needed in practicing the treatment of cancers comprising CpG molecules. Thus, the instant application gives no data relevant to the use of the nucleic acids mentioned in the claims in any in vivo method to control or affect any of the conditions mentioned in the claims. One of ordinary skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids.

Therefore after a fresh consideration of the claims and the evidence provided, the rejection is maintained.

Conclusion

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

November 4, 2008

/David J Blanchard/
Primary Examiner, Art Unit 1643